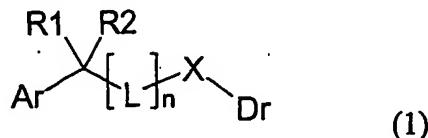


CLAIMS

1. A compound of formula (1), or a pharmaceutically acceptable salt thereof,

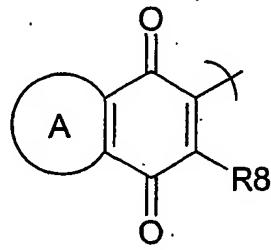
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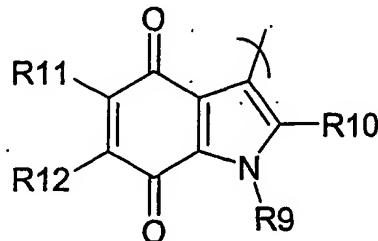
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wherein:

- Ar is a substituted aryl or heteroaryl group bearing at least one nitro or azido group or is a group of formula (2) or (3)



(2)



(3)

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- R<sub>1</sub> and R<sub>2</sub>, which may be the same or different are independently optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, aryl, COR<sub>3</sub> or, together with the intervening carbon atom, form an optionally substituted heterocycloalkyl or carbocyclic ring;
- L is -OC(O)- or -OP(O)(OR<sub>6</sub>)-;
- n is 0 or 1;
- 20 - X is O, S, NR<sub>7</sub> or a single covalent bond;
- R<sub>3</sub> is OR<sub>4</sub> or NR<sub>4</sub>R<sub>5</sub>;
- R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are each independently hydrogen or optionally substituted alkyl or,  
where R<sub>3</sub> is NR<sub>4</sub>R<sub>5</sub>, R<sub>4</sub> and R<sub>5</sub> can be joined to form, together with the intervening nitrogen atom, a heterocycloalkyl ring;
- 25 - R<sub>8</sub> is hydrogen, alkoxy or dialkylaminoalkyl;

- R<sub>9</sub> is optionally substituted alkyl;
- R<sub>10</sub> is hydrogen, alkyl, alkoxy or dialkylaminoalkyl;
- R<sub>11</sub> and R<sub>12</sub> are independently hydrogen, alkyl, alkoxy, thioalkoxy, amino, alkylamino, dialkylamino, morpholino, piperidino, piperazino or 1-aziridinyl;

5    - A is an optionally substituted aryl or heteroaryl ring; and

- Dr is a moiety such that DrXH represents a cytotoxic or cytostatic compound.

2.    A compound according to claim 1, wherein the alkyl, alkenyl and alkynyl groups in the R<sub>1</sub> to R<sub>12</sub> substituents are unsubstituted or substituted with 1, 2 or 3

10    unsubstituted substituents selected from halogen, amino, mono(C<sub>1</sub>-C<sub>4</sub> alkyl)amino, di(C<sub>1</sub>-C<sub>4</sub> alkyl)amino, hydroxy, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkylthio and (C<sub>1</sub>-C<sub>4</sub> alkyl)sulphonyl groups.

3.    A compound according to any one of the previous claims, wherein aryl and

15    heteroaryl groups in the Ar, A and R<sub>1</sub>, R<sub>2</sub> substituents are unsubstituted or substituted with 1, 2 or 3 unsubstituted substituents selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy, amino, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy and C<sub>1</sub>-C<sub>4</sub> haloalkoxy.

4.    A compound according to any one of the previous claims, wherein the

20    heterocycloalkyl ring and carbocyclic rings in the R<sub>1</sub> to R<sub>3</sub> substituents are unsubstituted or substituted with 1, 2 or 3 unsubstituted substituents selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy, amino, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy and C<sub>1</sub>-C<sub>4</sub> haloalkoxy.

25    5.    A compound according to any one of the previous claims, wherein R<sub>1</sub> and R<sub>2</sub>, together with the carbon to which they are attached, form a 3 to 10 membered heterocycloalkyl ring or a C<sub>3-10</sub> carbocyclic ring, which ring is unsubstituted or substituted by 1, 2 or 3 unsubstituted substituents selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy, amino, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy and C<sub>1</sub>-C<sub>4</sub> haloalkoxy.

6. A compound according to claim 5, wherein R<sub>1</sub> and R<sub>2</sub>, together with the carbon to which they are attached, form a 5 to 6 membered heterocycloalkyl ring, which ring is unsubstituted or substituted by one unsubstituted C<sub>1</sub>-C<sub>2</sub> alkyl group.

5 7. A compound according to any one of claims 1 to 4, wherein R<sub>1</sub> and R<sub>2</sub> are the same or different and each represent unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl, unsubstituted C<sub>1</sub>-C<sub>6</sub> alkenyl, unsubstituted C<sub>1</sub>-C<sub>6</sub> alkynyl, a COR<sub>3</sub> group, an unsubstituted phenyl group or a phenyl group which is substituted with 1, 2 or 3 unsubstituted substituents selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy, amino, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy and C<sub>1</sub>-C<sub>4</sub> haloalkoxy.

10 8. A compound according to claim 7, wherein R<sub>1</sub> and R<sub>2</sub> are the same or different and each represent unsubstituted C<sub>1</sub>-C<sub>4</sub> alkyl, unsubstituted C<sub>1</sub>-C<sub>4</sub> alkenyl, unsubstituted C<sub>1</sub>-C<sub>4</sub> alkynyl, a COR<sub>3</sub> group, an unsubstituted phenyl group or a phenyl group which is substituted with 1, 2 or 3 unsubstituted substituents selected from halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, hydroxy, amino, C<sub>1</sub>-C<sub>2</sub> haloalkyl, C<sub>1</sub>-C<sub>2</sub> alkoxy and C<sub>1</sub>-C<sub>2</sub> haloalkoxy.

15 9. A compound according to claim 7 or 8, wherein R<sub>3</sub> is hydroxy, unsubstituted C<sub>1</sub>-C<sub>4</sub> alkoxy or NR<sub>4</sub>R<sub>5</sub>, wherein R<sub>4</sub> and R<sub>5</sub> are the same or different and each represent hydroxy or unsubstituted C<sub>1</sub>-C<sub>4</sub> alkoxy, or R<sub>4</sub> and R<sub>5</sub> form, together with the nitrogen atom to which they are attached, a 3 to 10 membered heterocycloalkyl ring, which ring is unsubstituted or substituted by 1, 2 or 3 unsubstituted substituents selected from halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy, amino, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy and C<sub>1</sub>-C<sub>4</sub> haloalkoxy.

20 10. A compound according to claim 9, wherein R<sub>3</sub> is hydroxy, unsubstituted C<sub>1</sub>-C<sub>2</sub> alkoxy or NR<sub>4</sub>R<sub>5</sub>, wherein R<sub>4</sub> and R<sub>5</sub> are the same or different and each represent hydrogen or unsubstituted C<sub>1</sub>-C<sub>4</sub> alkyl.

11. A compound according to any one of claims 7 to 10, wherein R<sub>1</sub> and R<sub>2</sub> are the same or different and each represent unsubstituted C<sub>1</sub>-C<sub>2</sub> alkyl or an unsubstituted -CO<sub>2</sub>-(C<sub>1</sub>-C<sub>2</sub> alkyl) group.
- 5 12. A compound according to any one of the preceding claims wherein n is 0 and X is O or S.
- 10 13. A compound according to any one of claims 1 to 11, wherein n is 1 and X is NH.
- 15 14. A compound according to any one of claims 1 to 11 or 13, wherein n is 1 and L is -OC(O)- or -OP(O)(OR<sub>6</sub>), wherein R<sub>6</sub> is hydrogen or unsubstituted C<sub>1-6</sub> alkyl.
- 20 15. A compound according to claim 14, wherein L is -OC(O)-.
16. A compound according to any one of the previous claims, wherein Ar is a substituted aryl or heteroaryl group, which group carries one substituent selected from nitro and azido substituents and 0, 1 or 2 further unsubstituted substituents chosen from halogen, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy, amino, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy and C<sub>1</sub>-C<sub>4</sub> haloalkoxy substituents .
17. A compound according to claim 16, wherein Ar is a phenyl group or a 5-or 6-membered heteroaryl group, which group carries only one substituent which substituent is selected from nitro and azido substituents.
- 25 18. A compound according to claim 17, wherein Ar is an unsubstituted group selected from nitrophenyl, nitroimidazole, nitrothiophene and nitrofuryl groups.
19. A compound according to any one of the previous claims, wherein DrXH is selected from an anthracyclin antibiotic, an antimetabolite, a topoisomerase inhibitor, an inhibitor of mitosis, inhibitors of protein kinases and an antagonist of (6R)-5,6,7,8-tetrahydrobiopterin.

20. A compound according to claim 19, wherein DrXH is selected from doxorubicin, epirubicin, daunorubicin, 5-fluorouracil, 6- mercaptopurine, 6-thioguanine, cytarabine, gemcitabine, capecitabine, fludarabine, cladribine, 5-decitabine (5-aza-2'-deoxycytidine), troxacicabine (2'-deoxy-3'-oxacytidine), 5-azacytidine, 4'-thioaracytidine, tezacitabine, clofarabine, trimetrexate and methotrexate, etoposide and teniposide, topotecan, SN38, combretastatin A4, combretastatin A1, podophyllotoxin, vinblastine, vincristine vinorelbine, paclitaxel and docetaxel, an epothilone, deoxyepothilone B BMS 247550, a dolastatin derivative, a cryptophycin derivative, gefitinib, erlotinib, ZD6474 and AZD2171.

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21. A compound according to claim 20, wherein DrXH is combretastatin A4, etoposide, cytarabine or 6-mercaptopurine.

15 22. A compound according to any one of the previous claims which is 1-(4-Methoxy-3-(2-(5-nitrothiophen-2-yl)propan-2-yl)oxyphenyl-2-(3,4,5-trimethoxy)phenyl-Z-ethene, 1-(4-Methoxy-3-(2-(4-nitrophenyl)propan-2-yl)oxyphenyl-2-(3,4,5-trimethoxy)phenyl-Z-ethene, 9-(7,8-Dihydroxy-2-methyl-hexahydro-pyrano[3,2-d][1,3]-dioxin-6-yloxy)-5-{3,5-dimethoxy-4-[1-methyl-1-(4-nitrophenyl)-ethoxy]-phenyl}-5,8,8a,9-tetrahydro-5aH-furo[3',4':6,7]naphtho[2,3-d][1,3]dioxol-6-one, 6-(2-(4-nitrophenyl)propan-2-ylsulfanyl)-9H-purine, 1-(4-Methoxy-3-(1-methyl-4-(5-nitrothien-2-yl)piperidin-4-yl)oxycarbonyloxy)phenyl-2-(3,4,5-trimethoxy)phenyl-Z-ethene, 1-(4-Methoxy-3-(2-(1-methyl-2-nitroimidazol-5-yl)propan-2-yl)oxyphenyl-2-(3,4,5-trimethoxy)phenyl-Z-ethene, 6-(2-(5-nitrothien-2-yl)propan-2-ylsulfanyl)-9H-purine, N<sup>4</sup>-(2-(5-nitrothien-2-yl)prop-2-yl)oxycarbonyl-1-β-D-arabinofuranosylcytosine, 1-(3-(1-Ethoxycarbonyl-1-(5-nitrothien-2-yl)ethoxy)-4-methoxy-phenyl)-2-(3,4,5-trimethoxyphenyl)-Z-ethene and N-(2-{3-[1-Methyl-1-(5-nitro-thiophen-2-yl)-ethoxy]-phenyl}-ethyl)-acetamide, or a pharmaceutically acceptable salt thereof.

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23. A pharmaceutical composition comprising a compound according to any one of the previous claims, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

5 24. A compound according to any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, for use in the treatment of the human or animal body.

10 25. Use of a compound as defined according to any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prevention or treatment of a proliferative disorder.

26. Use according to claim 25, wherein the proliferative disorder is cancer, rheumatoid arthritis, psoriatic lesions, diabetic retinopathy or wet age-related macular degeneration.

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27. Use according to claim 25 or 26, wherein the proliferative disorder is a hypoxic disorder.

20 28. Use according to any one of claims 25 to 28, wherein the medicament is for use in the prevention or treatment of a solid tumour or leukaemia.

25 29. A method of ameliorating or reducing the incidence of a proliferative disorder as defined according to any one of claims 25 to 28 in a patient, which method comprises administering to said patient an effective amount of a compound as defined in any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof.

30 30. A method according to claim 29, which method comprises administering to said patient an effective amount of

(a) a compound as defined in any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof; and

(b) a reductase, an anti-body reductase conjugate, a macromolecule-reductase conjugate or DNA encoding a reductase gene.

31. A product containing
  - (a) a compound as defined in any one of claims 1 to 22, or a pharmaceutically acceptable salt thereof; and
  - 5 (b) a reductase, an anti-body reductase conjugate, a macromolecule-reductase conjugate or DNA encoding a reductase gene for the simultaneous, separate or sequential use in the treatment of a proliferative disorder as defined in any one of claims 25 to 28.